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EXAMINER	
DIBRINO, MARIANNE NMN	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/774,176	CARROLL ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37,39,41,48-51 and 53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37,39,41,48-51 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/18/07 has been entered.

Applicant's amendment and response filed 10/18/07 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election with traverse of Group I (currently claims 37, 39, 41, 48-51 and 53), and species of SEQ ID NO: 5 in responses filed 3/22/06 and 6/5/06 and in Applicant's amendment and response filed 9/15/06.

Claims 37, 39, 41, 48-51 and 53 are presently being examined.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 37, 39, 41, 48-51 and 53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir.1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the expression vector(s) recited in the instant claims.

The instant claims encompass an expression vector or a pair of vectors, including poxvirus vector(s) such as MVA, wherein the said vector(s) *comprise* a nucleotide sequence encoding (*i.e., comprising*) human 5T4 antigen that is *modified* to differ from any naturally occurring 5T4 antigen from any species and comprises an HLA CTL peptide epitope of 5T4 antigen, including one of SEQ ID NO: 5-17, and wherein the

modified human 5T4 antigen is a peptide fragment between 5 and 26 amino acid residues in length, and wherein the modification is any modification of any portion of human 5T4 antigen, and wherein the CTL peptide epitope may or may not be a subsequence of the human 5T4 protein and wherein the sequences flanking the N and C termini of said epitope may or may not be a subsequence of the human 5T4 protein, and wherein the modified 5T4 antigen is capable of inducing an anti-tumor immunotherapeutic response in a subject, including wherein the said response is a CTL or an antibody response, and including for claims 48-51 and 53 wherein the vectors are for priming and boosting an immune response in a subject.

As such, the claims are drawn to an expression vector comprising a nucleotide sequence encoding a peptide of undisclosed or partially disclosed structure. In addition, instant claim 39 is drawn to said expression vector wherein the modified human 5T4 antigen comprises a CTL epitope, but not necessarily a Th or B epitope, and produces an antitumor immunotherapeutic antibody response. Furthermore, the instant claims encompass said expression vector wherein the peptide fragment is 5, 6 or 7 amino acid residues in length, too small to be or to comprise a CTL epitope.

As the complete structures of the claimed peptides are not disclosed, among the distinguishing relevant identifying characteristics considered in this analysis are partial structure, physical and/or chemical properties, functional characteristics, known or disclosed correlation between structure and function, and method of making.

The specification discloses that human 5T4 is characterized by Myers *et al*, the sequence of which appears in GenBank at accession no. Z20983 and is set out as SEQ ID NO: 1 of the instant application (page 5 at lines 13-15). Evidentiary reference GenEmbl Accession No. Z209083 teaches the sequence of Accession no. Z29083, human 5T4 gene for 5T4 oncofetal antigen.

The specification discloses that a modified 5T4 antigen is a polypeptide that has been truncated, extended or otherwise mutated such that it differs from naturally occurring 5T4. The specification discloses that 5T4 peptides may be mutated by amino acid insertion, deletion or substitution, may be any length, but are advantageously between 5-25 amino acid residues, and preferably between 6 and 15 amino acid residues. The specification discloses that the peptides are able to bind HLA molecules and to induce CTL responses against wild-type 5T4 in subjects, often more effectively than full length 5T4 (page 5 at lines 22-32). The specification further discloses that human 5T4 consists of SEQ ID NO: 1, mouse 5T4 consists of SEQ ID NO: 2 and canine 5T4 consists of SEQ ID NO: 3, and that the invention comprises species and allelic variations of 5T4, as well as fragments, preferably distinct epitopes, and variants thereof comprising amino acid insertions, deletions or substitutions that retain the antigenicity of 5T4 (page 5 at lines 12-20).

It is noted by the Examiner that the elected species SEQ ID NO: 5 is a subsequence of the human 5T4 protein. Therefore instant claim 41 encompasses an expression vector wherein the modified 5T4 antigen comprises a peptide sequence selected from SEQ ID NO: 5 or any of the other recited SEQ ID NO that are unaltered subsequences of human 5T4 protein flanked by undisclosed sequence that are not contiguous flanking sequence from human 5T4 protein, *i.e.,* the human 5T4 antigen is modified by being truncated and optionally having flanking sequences not present in the human 5T4 protein.

As to the issue of "human 5T4 antigen...modified to differ from a naturally occurring 5T4 antigen," the specification discloses only three naturally occurring 5T4 antigens as enunciated supra, *i.e.,* that of SEQ ID NO: 1-3, or human, mouse and canine; *thus the instant specification discloses only two species of non-human naturally occurring 5T4 protein antigen.*

The specification discloses that MVA vectors comprising nucleic acid molecules that correspond to the coding sequence of human or mouse 5T4 were effective in raising a high titre of antibodies when administered to mice (Example 9), and that in mouse tumor models, mice vaccinated with MVA-h5T4 or MVA-m5T4 were able to mount anti-tumor activity when challenged with a syngeneic tumor line expressing the human or mouse 5T4 protein with resulting tumor retardation or lowered tumor burden (Examples 3-8).

The production of antibodies in mice injected with MVA vectors comprising nucleic acid molecules that correspond to the coding sequence of the entire human or mouse 5T4 proteins, said antibodies able to mount anti-tumor activity when challenged with a syngeneic tumor line expressing the human protein, is not representative of immunization with a subsequence or modified subsequence of a human 5T4 encoding nucleic acid molecule wherein the subsequence contains a CTL epitope along with undisclosed flanking sequences and wherein the cancer is established.

As to the issue of "*comprise and encodes*", the specification does not disclose wherein the vector(s) encode a nucleic acid sequence comprising one of SEQ ID NO: 5-17 with undisclosed flanking sequences, nor variants that are altered subsequences of 5T4 proteins, including those comprising undisclosed flanking sequences not in the protein of origin, nor species other than human, murine or canine. *Thus the specification does not provide a representative number of species, nor disclose the structure of the flanking sequences comprising one of SEQ ID NO: 5-17, nor the structure of altered subsequences of 5T4 proteins that correlate with the functional property of inducing an antitumor immunotherapeutic response, either a CTL response or an antibody response, as is required by the instant claims.*

In terms of being a CTL epitope, the art recognizes that the length of the peptide is important for binding to HLA (along with the presence of anchor (or "motif") amino acid residues present within the peptide). The peptides that bind to class I molecules have a predominant length, *i.e.,* a minimum of 8 or 9 amino acid residues for a class I MHC restricted T cell epitope peptide. A primary factor for this is that amino acid residues at the amino- and carboxy-termini of peptides binding to class I molecules interact with conserved amino acid residues in pockets ("A","F") located at opposite ends of the binding groove of the class I molecule, giving rise to a common orientation of the peptides in the binding site (Engelhard at page 14, column 1, lines 16-27, of record) Thus, the amino acid residues at the peptides' termini make a network of hydrogen bonds with conserved residues on the sides and bottom of the peptide binding groove of class I molecules. These interactions are important for holding the peptides in the binding groove and for stabilizing the complex (Guo *et al* at page 366, column 1 lines 1-10, of record) "...the preferred length (of the peptide) is determined by the minimum amount of peptide required to span the center of the binding site and optimize the interactions at the ends", but that the predominant length is 9 amino acid residues (Engelhard at page 14, column 1, lines 23-27, of record).

In addition, the art recognizes that flanking sequences influence the processing and presentation of CTL epitopes (Eisenlohr *et al*, Shastri *et al*, Bergmann *et al*, Wang *et al*, Perkins *et al*, Theoboald *et al* and Gileadi *et al*, all of record) and that immunodominance can be affected by the context of the epitope within the protein molecule and that junctional neoepitopes can be created (Perkins *et al,* of record) or that immunodominant epitopes can be completely silenced by contiguous sequences (Wang *et al,* of record). *The specification does not describe which flanking sequences would be permissive to allow the processing and presentation of CTL epitopes nor which flanking sequences correlate with the functional property of inducing an antitumor immunotherapeutic response.*

The specification does not provide a representative number of species of modified 5T4 antigen encoded for and comprised in an expression vector that confer the functional property of inducing an antitumor immunotherapeutic response. The specification provides no disclosure that modified 5T4 antigens encoded in the vector(s) of the claimed invention are immunogenic, either as CTL, Th or B cell epitopes. *In vivo* studies disclosed in the instant specification utilize whole unaltered human or murine 5T4 as enunciated supra.

Celis *et al* (of record) teach "In addition to MHC binding, other factors such as antigen processing, peptide transport and the composition of the T-cell receptor repertoire could determine whether peptides can function as effective CTL antigens."

Ochoa-Garay *et al* (of record) teach that "In summary, the results in this report indicate that the immunogenicity of a peptide cannot always be predicted from its affinity for class I or the presence of class I binding motifs. In addition, our data show that variables such as CTL precursor frequency, peptide hydrophobicity and stability can influence the *in vitro* induction of CTL responses" (especially page 279, last sentence and continuing onto page 280).

Thus, the evidentiary references underscore that structure in terms of possessing anchor residues and other residues permissive for MHC binding and/or high affinity binding do not necessarily correlate with the functional property of being immunogenic, and hence by extension, to being capable of inducing an antitumor immunotherapeutic response in a subject.

The specification provides no disclosure that the SEQ ID NO recited in instant claim 41 that were selected by prediction algorithm and shown to bind to HLA-A*0201 are immunogenic, *i.e.,* induce CTL, and can produce a clinical endpoint in inducing an anti-tumor immunotherapeutic response. Although the instant specification discloses that immunization with vector(s) encoding unmodified full-length human or murine 5T4 protein in mouse tumor models could produce a clinical response *in vivo*, there is no disclosure that the isolated SEQ ID NO can produce the clinical result, even if capable of inducing CTL, and thus there is no disclosure of what structure, including sequences flanking the said SEQ ID NO, correlate with producing the functional property of inducing an antitumor immunotherapeutic response.

Evidentiary reference Berger *et al* (Int. J. Cancer. 111: 229-237, 2004, of record) teach "The induction of tumor-specific T cells, however, is not necessarily associated with a clinical response" (column 1, page 229).

Evidentiary reference Gao *et al* (J. Immunother. 23: 643-653, 2000, of record) found that although anti-tumor CTL response was enhanced by immunization, the tumors failed to regress due to an association with lack of CTL migration to the tumor sites (abstract). Thus, Gao *et al* teach that activation of peptide epitope-specific CTL is not an appropriate endpoint.

Evidentiary reference Boon *et al* (Ann. Rev. Immunol. 2006, 24: 175-208, of record) teach "In conclusion, therapeutic success following vaccination may not depend on the number of T cells produced directly by the vaccine, *but rather on the production of a T cell clone with functional properties that enable it to migrate to the tumor and resist the local immunosuppressive environment long enough to initiate a regression process* " (Examiner emphasis, pages 193-194).

Thus, there is no description in the instant specification of which of the millions of modified 5T4 antigens encompassed by the claimed invention would be immunogenic and would be capable of inducing an antitumor immunotherapeutic response in a subject, nor which structures correlate with such functional properties. Nor does the specification provide a representative number of species.

In view of the aforementioned problems regarding description of the claimed invention, the specification does not provide an adequate written description of the invention claimed herein. See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1404-7 (Fed. Cir.1997). In University of California *v.* Eli Lilly and Co., 39 U.S.P.Q.2d 1225 (Fed. Cir. 1995) the inventors claimed a genus of DNA species encoding insulin in different vertebrates or mammals, but had only described a single species of cDNA which encoded rat insulin. The court held that only the nucleic acids species described in the specification (*i.e.,* nucleic acids encoding rat insulin) met the description requirement and that the inventors were not entitled to a claim encompassing a genus of nucleic acids encoding insulin from other vertebrates, mammals or humans, id. at 1240. The Federal Circuit has held that if an inventor is "unable to envision the detailed constitution of a gene so as to distinguish it from other materials. . .conception has not been achieved until reduction to practice has occurred", Amgen, Inc. *v.* Chugai Pharmaceutical Co, Ltd., 18 U.S.P.Q.2d 016 (Fed. Cir.1991). Attention is also directed to the decision of The Regents of the University of California *v.* Eli Lilly and Company (CAFC, July 1997) wherein is stated: "The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, as we have previously held, a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA." See Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606.

The instant disclosure does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera, including an expression vector(s) comprising a nucleic acid sequence encoding a human modified 5T4 antigen, said antigen that includes a polypeptide that has been truncated, extended or otherwise mutated, by amino acid insertion, deletion or substitution, such that it differs from any naturally occurring 5T4, variant or allele derived from any species. Since the disclosure fails to provide sufficient relevant identifying characteristics, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

Applicant's arguments in the amendment filed 10/18/07 have been fully considered, but are not persuasive.

Applicant's arguments are of record on pages 5-9 of the said amendment, briefly: (1) the claims are now directed to modified human 5T4 peptide fragments which are between 5 and 25 amino acid residues in length, (2) the specification discloses 13 different human 5T4 peptide fragments (SEQ ID NO: 5-17 and Examples 10 and 11) and 13 different murine 5T4 peptides (SEQ ID NO: 18-27) and these modified 5T4 peptides were identified through HLA ranking prediction algorithms known in the art, (3) the claimed vectors require that the 5T4 peptides are capable of inducing an anti-tumor immunotherapeutic response and this is important in that HLA peptide binding and stability are most influential factors correlating to CTL responses, and Applicant cites Overwijk *et al.* 1998 (J. Exp. Med. 188(2):277-286, IDS reference) in which an HLA binding program was used to predict peptide epitopes that induce anti-tumor CTL responses to gp100, and such CTL epitopes are within the top 2% of binding peptides (Applicant cites Parker *et al.* 1994, J. Immunol. 152: 163-175, IDS reference, for the latter point), (4) the gene based 5T4 approach detailed in the instant specification has been proven to break tolerance at both the antibody and T cell level without inducing autoimmune pathology in late stage colorectal cancer (Applicant cites Harrop *et al.* 2006, Clin. Cancer Res. 12(11): 3416-3424), (5) other studies have shown that the incidence of a 5T4 T cell response is statistically linked to clinical benefit (Applicant cites Harrop *et al.* 2007 Clin. Cancer Res. 13(15): 4487-4494, col. 1, para 2), thus providing evidence that 5T4 epitopes can be efficiently presented and are present on the surfaces of tumors, statistically linking 5T4 specific CTLs to providing a therapeutic effect, (6) clinical trials are in progress, and (7) subsequent work in WO 06/120473 notes that some peptides identified through algorithms are also candidate peptides identified through patient screening, notably, peptides 49, 142, 151, 176 and 183 corresponding to SEQ ID NO: 5, 9, 17, 7 and 15 of the instant specification.

In response to Applicant's arguments: (1) the claims are not directed to a contiguous subsequence of human 5T4 protein that is between 5 and 25 amino acid residues in length, but rather to a CTL epitope of human 5T4 protein that may or may not be modified from the originally present sequence and that may or may not comprise undisclosed flanking residues that are not contiguous subsequence of human 5T4 protein, (2) SEQ ID NO: 5-17 are subsequences of human 5T4 protein that are predicted to bind HLA-A2.1 based upon a prediction algorithm, and Example 11 discloses changing an amino acid residue in SEQ ID NO: 11 to increase its stability of binding to HLA-A2.1, however, the instant claims are not limited in scope to subsequences of human 5T4 protein and substitution variants thereof that increase binding stability to an HLA class I molecule, (3) Overwijk *et al.* 1998 do not teach peptide administration, nor a correlation between CTL that are adoptively transferred in their study and tumor regression or patient survival, *i.e.,* they do not correlate CTL generation and administration with inducing an antitumor immunotherapeutic response in a subject as is recited in the instant claims, and neither do Parker *et al*, and evidentiary reference Nijman *et al* cited herein teaches that the highest affinity peptides from self-proteins may not be the determinants that induce CTL (4) Harrop *et al.* 2006 show an association, not causation, of 5T4 antibody titer after injection with MVA-5T4 with increased time to progression and enhanced patient survival. They teach "There could conceivably be some third unmeasured factor which results in both a higher 5T4 antibody response (in those that do respond) and a higher survival." The instant claims are drawn to expression vector(s) comprising a nucleic acid sequence encoding a modified human 5T4 antigen that comprises a CTL epitope, not a Th epitope for antibody production. In addition, Harrop *et al.* 2006 was published after the effective filing date of the instant application. One is not required to provide written description for what was well known in the art at the time of invention, however, even if such description were provided by Harrop *et al.* 2006, the publication date of Harrop *et al.* 2006 is after the effective filing date of the instant application, (5) Harrop *et al.* 2007 teach that no correlation was observed between 5T4 –specific antibody responses and clinical benefit, although a correlation was noted with ELISPOT responses. Harrop *et al.* 2007 was also published after the effective filing date of the instant application, (6) clinical trials in progress after the effective filing date of the instant application do not provide written description regardless of what outcomes they have or have not, (7) WO 06/120473 does not teach a correlation with clinical response and has a publication date after the effective filing date of the instant application.

It is the Examiner's further position that a prima facie case of inadequate written description is set forth supra. The evidentiary references cited herein indicate that many factors influence immunogenicity of peptide sequences, including the context they are presented in in terms of flanking sequences, and that even when CTL epitopes are immunogenic, there is not a structure function correlation in the ability to induce an antitumor immunotherapeutic response in a subject.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 37, 39, 41, 48-51 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Starzynska *et al* (Eur. J. Gastroenterology & Hepatology 1998, 10(6): 479-484, IDS reference) in view of Gnjatic *et al* (Eur. J. Immunol. 1995, 25: 1638-1642), Theobald *et al* (J. Exp. Med. 1997, 185(5): 833-841), Vierboom *et al* (J. Exp. Med. 1997, 188(5): 695-704), Kobayashi *et al* (Cancer Res, 1998, 58: 296-301), Myers *et al* (J. Biol. Chem. 1994, 269(12): 9319-9324), Nijman *et al* (Eur. J. Immunol. 1993, 23: 1215-1219) and WO 98/56919 A2.

Starzynska *et al* teach that the expression of 5T4 antigen in cancer cells is correlated with poor short-term prognosis, as is accumulated expression of p53, with patients expressing the 5T4 antigen having poorer clinical outcome than those expressing the p53 antigen. Starzynska *et al* teach that the role of the 5T4 antigen in malignancy may be related to its function in influencing cell adhesion, shape and motility (especially page 483 at column 1 at the first three full paragraphs).

Starzynska *et al* do not teach an expression vector comprising a nucleotide sequence encoding human 5T4 antigen, wherein said human 5T4 antigen is modified to differ from a naturally occurring 5T4 antigen and comprises a CTL epitope of 5T4 antigen, and wherein the modified human 5T4 antigen is a peptide fragment of between 5 and 25 amino acid residues in length and is capable of inducing an antitumor immunotherapeutic response in a subject.

Gnjatic *et al* teach that antibodies to p53 have been detected in patients with various cancers, but very little is known about CTL response to p53 *in vivo*. Gnjatic *et al* further teach that p53 peptides could be presented to the immune system by tumor cells and thus might be a suitable target antigen for developing an immunotherapy against tumors using CTL. Gnjatic *et al* teach mapping and ranking of potential CTL epitopes in the p53 protein by synthesizing peptides of 8-11 residues that contain putative anchor motifs required for binding to common HLA class I molecules and testing them for their capacity to bind to HLA-A1, -A2 –B7 or -B8 molecules (especially abstract and introduction sections).

Theobald *et al* teach elevated levels of the p53 protein occur in about 50% of human malignancies, which makes it an excellent target for broad-spectrum T cell immunotherapy of cancer. Theobald *et al* further teach that circumvention of functional tolerance of high avidity CTL may be a necessary prerequisite for optimizing immunotherapy against HLA-A2.1-restricted p53 epitopes in humans. Theobald *et al* teach that the presence of low avidity CTL could provide an opportunity for immunotherapy of tumors that express high levels of p53, but that due to variability of the effect observed on the repertoire by self tolerance to different peptides, as well as variability of responsiveness due to different modes of immunization, it is likely that the success of the immunotherapy directed towards self-proteins will require careful examination of responses to each MHC-peptide complex (especially abstract and last paragraph of reference).

Vierboom *et al* teach self antigens can serve as targets for CTL-mediated destruction of tumors (first paragraph of reference). Vierboom *et al* further teach that activation of CTL to autoantigens is feasible in cancer patients as evidenced by the recent analyses of responses against melanoma-associated antigens and against p53, and CTL from healthy donors reactive against tyrosinase or wt p53 can be aroused from an unresponsive state by appropriate *in vitro* stimulation (last two paragraphs of reference).

Kobayashi *et al* teach CD4 and CD8 T cell responses from tyrosinase, a differentiation antigen that is a normal self-protein (like 5T4) expressed in some normal tissues as well as in melanomas, and further teach the value of identifying epitopes for design of a tumor vaccine for immunotherapy (especially abstract, introduction and first sentence of discussion).

Myers *et al* teach the DNA and protein sequence of human 5T4 antigen (see entire reference, especially Figure 2).

Nijman *et al* teach the binding motif for HLA-A2.1 is Leu, Ile or Met at position 2 and a hydrophobic aliphatic amino acid residue at the carboxy terminus of the peptide (especially spanning pages 1215 and 1216). Nijman *et al* teach that the peptides that are nonamers as well as those longer than nine amino acid residues can also bind to MHC molecules (especially paragraph spanning pages 1215 and 1216). Nijman *et al* further teach a method of screening peptides of a protein for peptide subsequences with anchor residues at the anchor positions for their ability to bind to HLA-A2.1 (especially page 1216 at the second column).

WO 98/56919 A2 teaches vaccination regimes that employ a priming vector and a boosting vector, the boosting and/or priming vector(s) comprising a non-replicating or replication-impaired pox virus vector carrying at least one of the same CD8 T cell epitope, *i.e.,* a CTL epitope (entire reference, especially abstract and claims). WO 98/56919 A2 teaches that non-replicating and replication-impaired strains of poxvirus provide vectors which give an extremely good boosting effect to a primed CTL response, and this effect is observed with tumor antigens (page 8 at lines 13-21). WO 98/56919 A2 teaches that the very high efficacy of non-replicating agents is observed in both priming and in boosting a CTL response (entire reference, especially paragraph spanning pages 9-10). WO 98/56919 A2 teaches that most preferably, the MVA strain of vaccinia is used (entire reference, especially page 11 at lines 17-23).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have identified potential CTL epitopes as per the methodology taught by Gnjatic *et al* for a tumor self protein p53 (the p53 also taught by Theobald *et al* and by Vierboom *et al* for which CTL epitopes were discovered, another self protein tyrosinase taught by Kobayashi *et al* against which CD4 and CD8 T cell responses were noted) and/or Nijman *et al,* but from the another tumor self protein, the human 5T4 protein taught by Starzynska *et al*, the sequence of which is taught by Myers *et al*, and to have produced priming and boosting vectors, including MVA, comprising nucleic acid sequence(s) encoding the potential human 5T4 CTL epitopes as per the teaching of WO 98/56919 A2 for other tumor antigens.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to generate reagents for use in research into induction of CTL responses by potential 5T4 CTL epitopes because: (1) Starzynska *et al* teach that the expression of 5T4 antigen in cancer cells is correlated with poor short-term prognosis, as is accumulated expression of p53, (2) the secondary references teach this process for the self protein p53, address the issue of overcoming tolerance, that self antigens can serve as targets for CTL-mediated destruction of tumors and emphasize the value of identifying epitopes for design of a tumor vaccine for immunotherapy (Gnjatic *et al* teach mapping and ranking of potential CTL epitopes in the p53 protein by synthesizing peptides of 8-11 residues that contain putative anchor motifs required for binding to common HLA class I molecules and testing them for their capacity to bind to HLA-A1, -A2 –B7 or -B8 molecules in order to research the capacity of this self protein to elicit CTL, Theobald *et al* teach elevated levels of the p53 protein occur in about 50% of human malignancies, which makes it an excellent target for broad-spectrum T cell immunotherapy of cancer, Vierboom *et al* teach that activation of CTL to autoantigens is feasible in cancer patients as evidenced by the recent analyses of responses against melanoma-associated antigens and against p53, and CTL from healthy donors reactive against tyrosinase or wt p53 can be aroused from an unresponsive state by appropriate *in vitro* stimulation, and Kobayashi *et al* teach CD4 and CD8 T cell responses from tyrosinase, a differentiation antigen that is a normal self-protein expressed in some

normal tissues as well as in melanomas, as well as the value of identifying epitopes for design of a tumor vaccine for immunotherapy), (3) Theobald *et al* teach that due to variability of the effect observed on the repertoire by self tolerance to different peptides, as well as variability of responsiveness due to different modes of immunization, it is likely that the success of the immunotherapy directed towards self-proteins will require careful examination of responses to each MHC-peptide complex, and (4) WO 98/56919 A2 teaches a vector system comprising non-replicating or replication-impaired pox virus such as MVA, that provide extremely good efficacy and safety in priming and boosting a CTL response.

Claim 41 is included in this rejection because SEQ ID NO: 5 would be generated as a potential CTL epitope since it has the anchor residues (bolded) for binding to HLA-A2.1 taught by Nijman et al, *i.e.*, FLTGNQFAV.

With regard to the limitation "is modified to differ from a naturally occurring 5T4 antigen," the instant claims are included in this rejection because the specification discloses that a modified 5T4 antigen is a polypeptide that has been truncated, extended or otherwise mutated such that it differs from naturally occurring 5T4 and that naturally occurring 5T4 is a protein as enunciated at item # 5 supra (the art peptide(s) of the combined references are truncated from the full length protein).

In addition, with regard to the limitation "is capable of inducing an antitumor immunotherapeutic response in a subject," the claimed vector and pair of vectors appear(s) to be similar to the vector and pair of vectors of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to that of the prior art, the burden is on Applicant to show an unobvious distinction between the composition of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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1/04/08

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